Azadirachta indica: A Source of Insect Feeding Inhibitors and Growth Regulators

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AZADIRACHTA INDICA: A SOURCE OF INSECT FEEDING INHIBITORS AND GROWTH REGULATORS

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ABSTRACT

Nontoxic, environmentally sound methods of pest control are of prime importance. For this reason neem tree components have been suggested as insect feeding inhibitors and growth regulators for 16 years. The activity of neem components upon Acari, Insecta, and Nematoda has been compiled. Some of these components, such as meliantriol, azadirachtin, and salannin, have been obtained in pure form. The structures of these triterpenoids along with the structures of other untested triterpenoids from neem have been incorporated into this review. All of these structures can serve as model compounds for the synthesis of commercially feasible insect feeding inhibitors and growth regulators to control larval and adult forms of stored-grain pests, termites, grass-hoppers, locusts, and nematodes.

KEYWORDS: *Azadirachta indica*, neem, insect feeding inhibitors, growth regulators, meliantriol, azadirachtin, salannin, stored-grain pests.

INTRODUCTION

The search for environmentally sound methods for controlling insect pests is being carried out in many laboratories. It is a search of great importance when one considers the alternatives: pollution, lack of species specificity, and development of insect resistance. One area of investigation in this search is the examination of plants for secondary metabolites that may have insect-repelling, insecticidal, antihormonal, or antifeeding characteristics (39). Such materials could serve as models for the synthesis of substances to be used with other agents in biologically sound integrated pest management systems.

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Feeding inhibition of pest insects is of utmost importance to the long-range research goals of this laboratory. The terms used to describe feeding inhibition (antifeedant activity) seem to fall into three categories: the repellent which actively repels the insect before contact, the suppressant which suppresses feeding by the insect after contact, and the deterrent which deters feeding after making contact. Some classify the last two terms as rejectants (9). Others do not consider antifeedants as repellents because they believe that insects are not driven away by antifeedants (102). However, there seem to be two types of repellents: olfactory and gustatory. Olfactory repellents in the vapor phase stimulate olfactory receptors and drive the insect away from the treated material. Gustatory repellents act upon receptors, which are not normally sensitive to vapors but are sensitive to feeding (68). Thus, a gustatory repellent could easily be called an antifeedant. All these terms, however, are used interchangeably (50).

The neem tree, Azadirachta indica A. Juss,[2/] is a source of insect feeding inhibitors and growth regulators belonging to the order of Meliaceae. It grows 40 to 60 feet tall in the arid parts (71) of India and Burma, and was introduced into the arid regions of Africa during the last century as an ornamental avenue tree. It grows in poor, dry soil and tolerates heat well, but it will not tolerate excessive cold or frost. The many common names for neem in different languages indicate that it is found in many countries (29, 43, 73).

DISCUSSION

The uses of neem are mentioned in the earliest Sanskrit medical writings (72). However, it was Pradhan et al. (66) who first reported on the repellent properties (now called suppressant) of neem for desert locust adults after using a 0.001 percent aqueous suspension of ground neem kernels. In 1962, field tests were carried out in Delhi, India, where a 0.1 percent aqueous ground neem kernel suspension was sprayed on different crops at 300 to 600 liters per hectare. Although locusts collected on the treated crops, no feeding was observed (63). This effect lasted for 2 to 3 weeks. Thus, neem kernels provided a far more potent weapon than strong insecticides to Delhi farmers, because locusts were able to consume insecticide-treated crops before succumbing (64). No phytotoxicity from the neem suspension was observed at concentrations as high as 0.5 percent sprayed on cabbage, tomato, peas, onion, cucurbits, wheat, tobacco, rose castor, litchi, fig, citrus, pomegranate, and mango (66).

Table 1 lists the insects, nematodes, and a mite upon which neem and some of its components have been tested and indicates the modes of action--feeding inhibition, growth regulation, toxicity, and aphicidal activity--for each species. In addition to these activities, two other neem components, nimbin and nimbidin, have been found to have antiviral activity against potato virus X(PVS) (89, 98), vaccinia virus, and fowl-pox virus (74). Neem has also been

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2/ Also referred to as Melia azadirachta L., M. indica Brandis, Margosa tree, or Indian lilac.

found to stabilize residues of pyrethrins for longer activity (1) and to have a synergistic action with custard apple against *Callosobruchus chinensis* (Lucas), *Rhyzopertha dominica* (F.), and *Musca domestica nebulo* F. (69).

Three feeding inhibitory triterpenoids have been isolated from neem. They are meliantriol (36) (fig. 1), salannin (20, 21, 101) (fig. 4b), and azadirachtin (5, 6, 7, 100, 104) (fig. 3e). Insects and nematodes tested with one or more of these compounds are indicated in table 1. Recent studies with these triterpenoids indicate good feeding inhibition with azadirachtin or salannin against the striped cucumber beetle (77) and the Japanese beetle (33) in laboratory and field tests. Salannin also acts as a feeding inhibitor for California red scale (48) and *Locusta* (4), while azadirachtin is a feeding inhibitor at 0.35 parts per million for fall armyworm (100) and a growth regulator (chitin inhibition) for the large milkweed bug (75).

The insect growth-regulating activity of neem is probably due to azadirachtin, since it is structurally similar to insect ecdysones (51). Robbins et al. (78) showed that ingestion of ecdysone analogs caused inhibition of insect growth and development in the tobacco hornworm. This type of activity is just one added benefit to the feeding inhibition activity possessed by neem.

Another benefit is the translocation in plants of azadirachtin and possibly other components of neem extracts. Young bean plants grown in soil that was treated with azadirachtin showed little damage by desert locust, and bean seedlings grown from seeds soaked in azadirachtin solutions were protected against damage by desert locust adults for 1 week after germination in cage feeding tests (15). Systemic uptake without phytotoxicity has also been demonstrated in wheat, barley, rice, sugarcane, grass, tomato, cotton, chrysanthemums, and the small spindle tree (73).

Table 1.--Arthropods and nematodes evaluated with neem (*Azadirachta indica*) for feeding inhibition (FI) and growth regulation (GR)1/

Scientific name	Common name	Activity2/	Reference
ARTHROPODA			
Acari			
† *Panonychus citri* (McGregor)	citrus red mite	FI, (-)FI†	23,48
Insecta			
	Coleoptera		
*† *Acalymma vittatum* (F.)	striped cucumber beetle	FI	77
Anthrenus flavipes LeConte	furniture carpet beetle	FI	29
Aulacophora foveicollis L.	red pumpkin beetle	FI	8,63,64,67,73
Callosobruchus chinensis (Lucas)	a seed weevil	FI	29
C. maculatus (F.)	cowpea weevil, pulse beetle	FI	27,63,64,81
Carabidae-Fam.	ground beetle in tobacco	FI	29
Carpophilus hemipterus (L.)	driedfruit beetle	FI	23
Cryptolestes pusillus (Schönherr)	flat grain beetle	FI	29,32,81
* *Epilachna varivestis* Mulsant	Mexican bean beetle	GR	93,95
Lasioderma serricorne (F.)	cigarette beetle	FI	81
Latheticus oryzae Waterhouse	longheaded flour beetle	FI	81
* *Leptinotarsa decemlineata* (Say)	Colorado potato beetle	FI, GR	82,94
Oryzaephilus surinamensis (L.)	sawtoothed grain beetle	(-)FI	81
*† *Popillia japonica* Newman	Japanese beetle	FI	33,34
Rhyzopertha dominica (F.)	lesser grain borer	FI	16,24,26,64,73,81
Scarabaeidae-Fam.	chafer grub in tobacco	FI	29
Sitophilus oryzae (L.)	rice weevil	FI	26,63,64,68,73,81
Stegobium paniceum (L.)	drugstore beetle	FI	29
Tribolium castaneum (Herbst)	red flour beetle	FI	24,63,68,73,81
T. confusum Jacquelin duVal	confused flour beetle	FI	29
Trogoderma granarium Everts	khapra beetle	FI	16,24,26,63,64,73, 80,81

		Diptera		
*†	*Aedes aegypti* (L.)	yellowfever mosquito	(-)FI	83
	Anopheles spp.	—	GR	73
	Atherigona soccata Rondani	sorghum shoot fly	FI	28
	Hydrellia	whorl maggot	(-)FI	29
	Musca	—	GR	73
†	*Musca domestica* L.	house fly	FI	101
	Stomoxys	—	GR	73
		Hemiptera (Heteroptera)		
	Antestiopsis orbitalis bechuana (Kirk)	coffee bug, shield bug	GR	38,51,101
*	*Dysdercus suturellus* (Herrich-Schäffer)	cotton stainer	GR	73,79
*	*Oncopeltus fasciatus* (Dallas)	large milkweed bug	GR	75
	Piesma quadratum Fieb	beet leaf bug	GR	93
	Urentius hystricellus (Richter)	Bringle lace wing	FI	29,73
		Hemiptera (Homoptera)		
	Aleurothrixus floccosus (Maskell)	wooly whitefly	FI	23
†	*Aonidiella aurantii* (Maskell)	California red scale	FI	23,48
	A. citrina (Coquillett)	yellow scale	FI	23
	—	aphids	FI	29
	Aphis gossypii Glover	melon aphid, cotton aphid	FI	29,73
	A. umbrella (Boerner)	—	FI	73
	Brevicoryne brassicae (L.)	cabbage aphid	Aphicidal	29
	Cicadellidae	cicadellids	FI	29
*	*Myzus persicae* (Sulzer)	green peach aphid	(-)FI	9
	Parasaissetia nigra (Nietner)	nigra scale	FI	29,73
	Planococcus citri (Risso)	citrus mealybug	(-)FI	23
	Rhopalosiphum nymphaeae (L.)	waterlily aphid, singhara aphid	Aphicidal	17
		Isoptera		
	Microtermes sp.	—	Toxic	29
*	*Reticulitermes santonensis*	Mediterranean moist wood termite	(-)FI	6
*	*Reticulitermes* sp.	—	FI	104

Table 1 - continued.

Scientific name	Common name	Activity	Reference
	Lepidoptera		
Achaea janata (L.)	croton caterpillar	FI	73
Agrotis ipsilon (Hufnagel)	black cutworm	FI	73
Amsacta moorei (Butler)	hairy caterpillar	FI	62,73
Atteva fabriciella Swederus	—	FI	73
Boarmia (Ascotis) selenaria (Denis & Schiffermüller)	giant looper	FI, GR	41
—	climbing cutworm	Toxic	29
Corcyra cephalonica (Stainton)	rice moth	FI	32,81
—	cotton boll worm	Toxic	29
Diacrisia obliqua (Walker)	—	FI	73
Earias insulana (Boisduval)	spiny bollworm	FI	40
Ephestia cautella (Walker)	almond moth	FI	81
Euproctis fraterna (Moore)	—	FI	28
E. laniata Hampson	castor hairy caterpillar	FI	2,3,4,5,67
Eupterote mollifera Walker	—	FI	73
* Galleria mellonella (L.)	greater wax moth	FI	104
* Heliothis virescens (F.)	tobacco budworm	FI, GR	79,104
* Hypsipyla grandella (Zeller)	—	FI	82
Indarbela quadrinotata (Walker)	bark eating caterpillar	Toxic	29
—	late stem borer	Toxic	29
—	leaf roller	Toxic	29
Lymantria dispar (L.)	gypsy moth	GR	91
* Mamestra brassicae (L.)	—	(-)FI	82
Nephantis serinopa Meyrick	—	FI	28
* Pieris brassicae (L.)	cabbage moth, cabbage white	GR	73,79,82,104
Plusia peponis (F.)	—	FI	73
* Plutella xylostella (L.)	diamondback moth	FI, GR	73,79,93,104
Sitotroga cerealella (Olivier)	Angoumois grain moth, paddy moth	FI	29
Spodoptera exigua (Hübner)	—	FI	73
*† S. frugiperda (J. E. Smith)	fall armyworm	FI*,(-)FI†	76,100
S. litura (F.)	tobacco caterpillar	FI	25,63,64,65,67
Utetheisa pulchella (L.)	—	FI	64,73

	Orthoptera		
Acrida exatana Walker	—	FI	64,65,73
Chrotogonus trachypterus Blanchard	surface grasshopper, toka	FI	29
Chrotoicetes terminifera	—	FI	73
† Locusta	—	FI	4
Locusta migratoria (L.)	migratory locust	FI	63,64,67,73,90
—	North American grasshoppers	(-)FI	49
Poecilocerus pictus	Ak grasshopper	FI	63,64,67
*†† Schistocerca gregaria Forsk	desert locust	FI	5,6,7,15,17,35, 36,63,64,66,67, 73,81,90,104
NEMATODA			
Hoplolaimus indicus Sher., 1963	—	GR	30
Meloidogyne incognita (Kofoid & White, 1919) Chitwood, 1949	—	GR	30
* Pratylenchus brachyurus (Godfrey, 1929) Filipjev & Schuurmans Stekhoven, 1941	—	FI	11,15,73
Rotylenchulus reniformis Linford & Oliveira, 1940	—	GR	11,30,99
Tylenchorhynchus brassicae Siddiqi, 1961	—	GR	30

1/ * Tested with azadirachtin (101).
† Tested with salannin (20,21).
†† Tested with meliantriol (36).

2/ (-) = negative response.

The structures of components of neem related to the three feeding inhibitors, meliantriol, azadirachtin, and salannin appear in figures 2, 3, and 4. These related components have not been tested for feeding inhibition or growth regulation. However, since they possess structures similar to the three mentioned feeding inhibitors, it is likely that they would possess some activity.

The biosynthetic pathway to these compounds involves cyclization of squalene and rearrangement to give (20S)-tirucallol or (20R)-euphol. These epimers are precursors of limonoids. (20S)-Tirucallol is the precursor of the meliane limonoid, meliantriol, in figure 1. Skeletal rearrangement of (20R)-euphol to the hypothetical intermediate apo-euphol will then give rise to the meliacin limonoids in figures 2, 3, and 4. Those compounds from neem which have the A, B, and C rings intact, and thus retain the apo-euphol basic structure, appear in figure 2 and belong to the gedunin group. Biosynthetic oxiation of apo-euphol leads to intermediate precursors (fig. 3) and then to the c-seco meliacin limonoids (fig. 4) (103).

There are also a number of other ill-defined crude materials from neem such as nimbidin T (63), thionimone (8, 30, 73), nimatone (72), nimbidol (86), and nimbidin (44, 45, 72, 84, 86) which have appeared in the literature with mention of insect feeding inhibition and growth regulation. Mention of hydrolysis products from these materials such as neo-nimbidin, nimbidic acid (45, 46, 86), nimbidinic acid, neonimbidin (86), and nimbidinin (44) also appears, but most of these materials have not been tested. Other components which have been isolated from neem are β-sitosterol (3, 70), 24-methylenecyclo=artanol (70), fatty acids (92), and the flavanoids: quercetin-2-galactoside (3, 96), kaempferol-3-glucoside (47, 96), and myricetin-3'-L-arabinoside (96).

The use of neem and its products as a source of insect feeding inhibitors and growth regulators is naturally dependent upon its toxicity and impact on the environment. Neem may be nontoxic to warm-blooded animals--the neem fruit is a favorite food for birds and neem twigs have long been used as chewing sticks to prevent tooth infection (51). However, neem products do have various pharmacological actions (86) which must be considered.

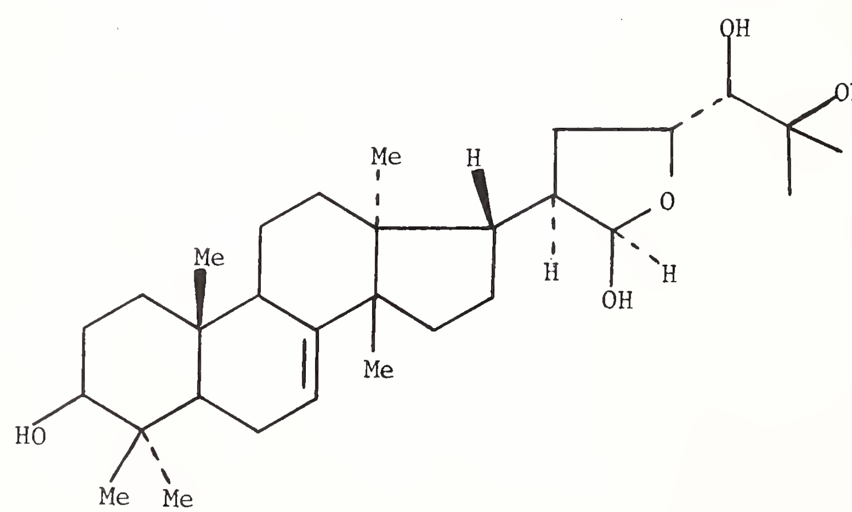
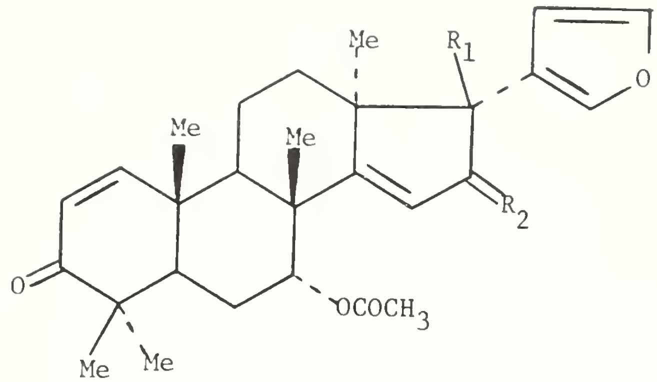


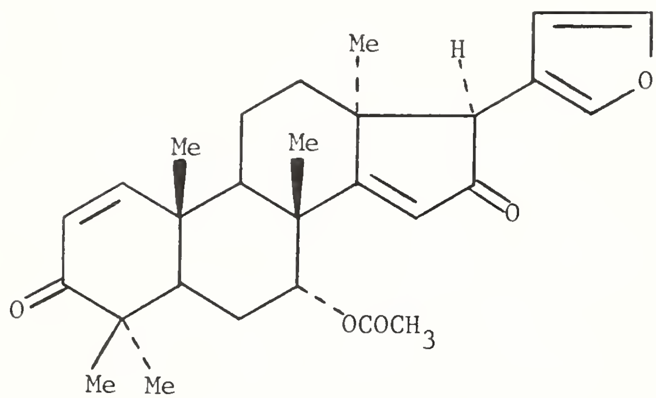
Figure 1.--Meliantriol (36).



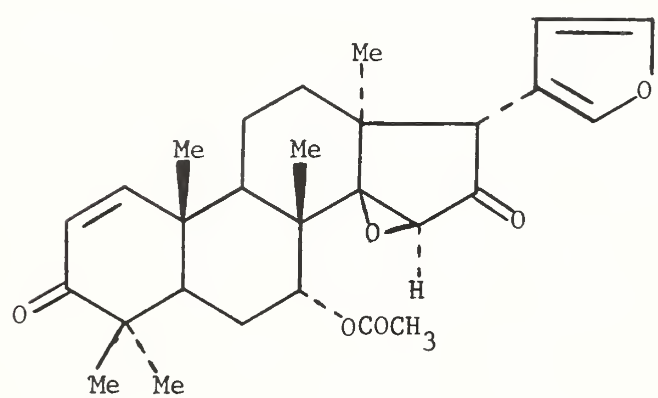
a R_1 = H, R_2 = 2H azadirone (35, 37)

b R_1 = H, R_2 = O azadiradione (31, 35, 37, 87)

c R_1 = OH, R_2 = O 17-β-hydroxy-azadiradione (31, 85)

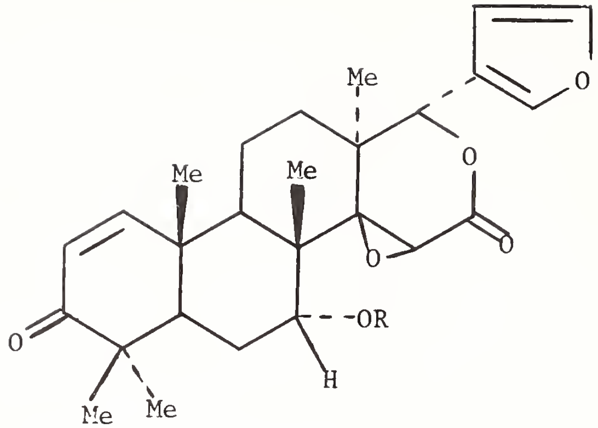


d 17-epi-azadiradione (31)



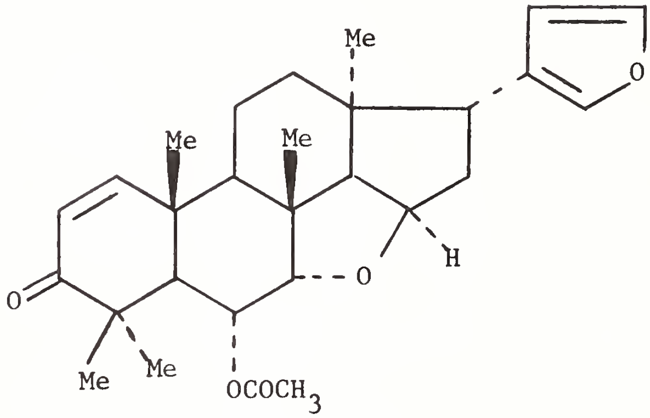
e epoxyazadiradione (nimbinin) (10, 35, 37, 46, 53, 56, 58, 59, 84, 86, 88, 105)

Figure 2.--Gedunin group.

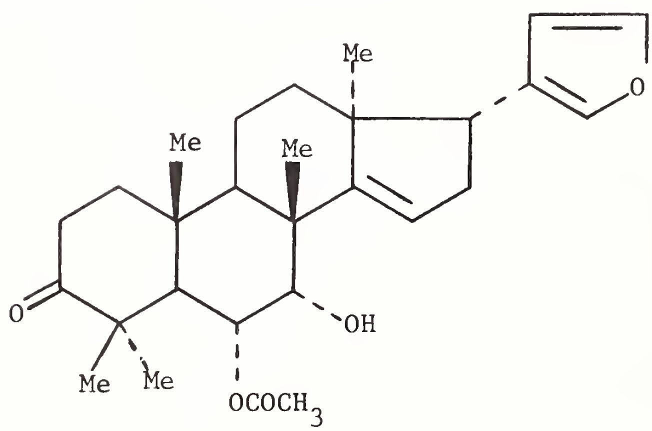


$\underline{f}$ R = $COCH_3$ gedunin (13, 35, 37)

$\underline{g}$ R = H 7-deacetoxy-7-α-hydroxygedunin (35, 37)

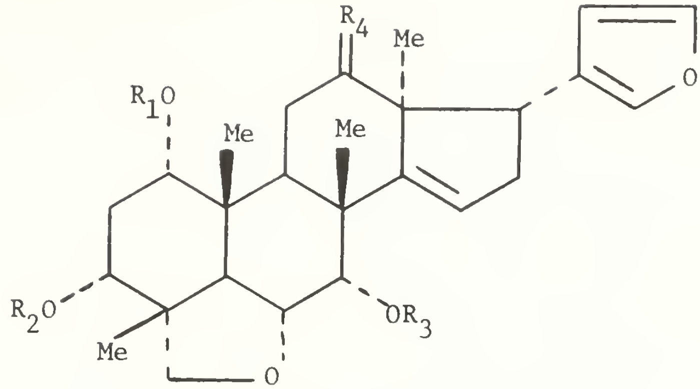


$\underline{h}$ vepinin (59)



$\underline{i}$ meldenin (10)

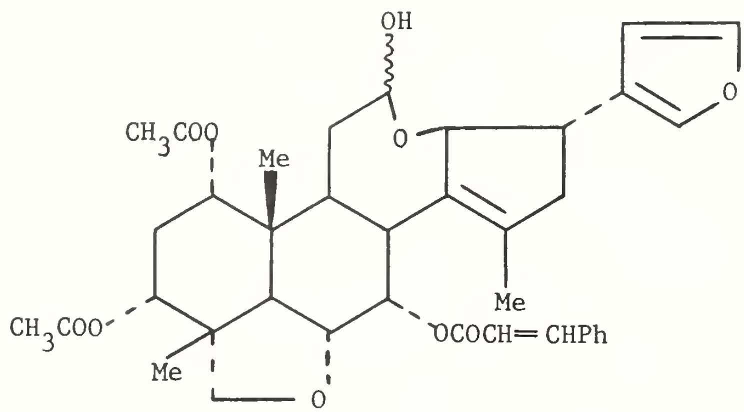
Figure 2.--Gedunin group (con.).



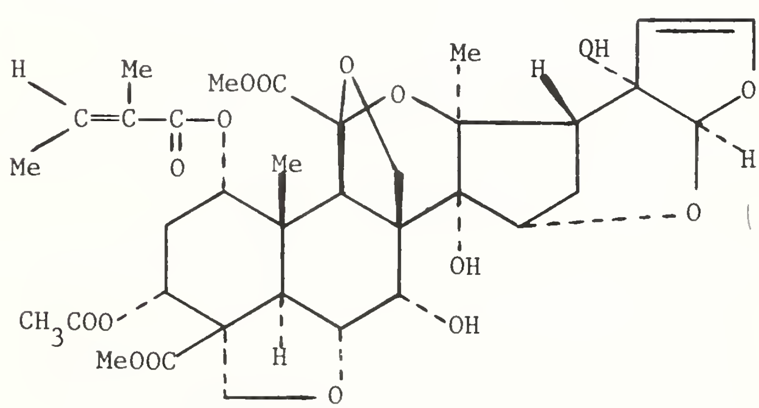
a $R_1 = R_2 = R_3 = H$, $R_4 = 2H$ vilasinin (61)

b $R_1 = R_2 = R_3 = H$, $R_4 = O$ nimbidinin (45, 46)

c $R_1 = R_2 = COCH_3$, $R_3 = COCH{=}CHPh$, $R_4 = 2H$ nimbolin A (13)

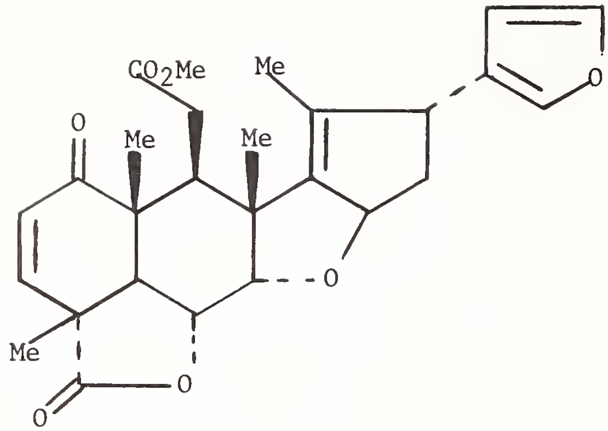


d nimbolin B (13)

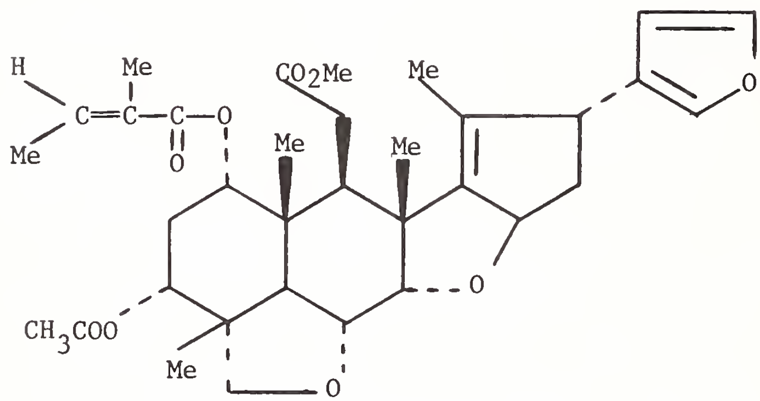


e azadirachtin (5, 6, 7, 100, 104)

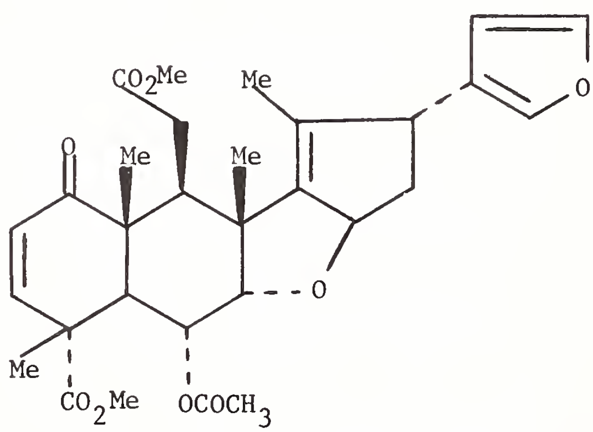
Figure 3.--Precursors of C-seco meliacins.



a nimbolide (12, 14)



b salannin (20, 21)



c nimbin (12, 19, 22, 42, 52, 53, 54, 55, 56, 57, 60, 72, 84, 98, 105

Figure 4.--C-seco meliacins.

Although neem is susceptible to attack by some insect pests (table 2) (29), it seems to offer an effective way of controlling larval and/or adult forms of stored-grain pests, termites, grasshoppers, locusts, and nematodes. Since the neem tree grows abundantly (71), its ground parts could be used until a commercial synthetic feeding inhibitor is available. Compounds similar in structure to those in figures 1-4 should be synthesized, but, of course, they must be simple enough to make them commercially feasible as insect feeding inhibitors and growth regulators.

Table 2.--Pests of neem

Scientific name	Common name	Reference
Acari		
Calepiterimerus azadirachta	eriophyid mite	97
Insecta		
	Coleoptera	
Araecerus fasiculatus (De Geer)	coffee bean weevil, anthribid fruit borer	97
Cryptocephalus ovulus Suffr.	—	97
Holotrichia consanguinea Blanchard	white grub beetle	18
H. insularis Brenske	white grub beetle	18
H. serrata (F.)	white grub beetle	18
	Hemiptera (Heteroptera)	
Helopeltis antonii Signoret	mirid bug	97
	Hemiptera (Homoptera)	
Pulvinaria maxima Green	mealy scale	97
	Lepidoptera	
Laspeyresia aurantianna Collar	—	97
	Orthoptera	
Orthacris simulans	—	97

ACKNOWLEDGMENTS

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